

The Claims

What is claimed is:

1. A method of treating an age-related behavioral disorder in a companion animal comprising administering to a companion animal in need of such treatment a therapeutically effective amount of an acetylcholinesterase inhibitor.

2. The method of claim 1 wherein the age-related behavioral disorder is cognitive dysfunction syndrome or involutive depression.

3. A method of improving the cognitive processing of a companion animal comprising administering to a companion animal in need of such improvement an amount of an acetylcholinesterase inhibitor sufficient to improve cognitive processing.

4. A method of treating memory loss in a companion animal comprising administering to a companion animal in need of such improvement an amount of an acetylcholinesterase inhibitor sufficient to improve cognitive processing.

5. A method of treating disorientation or confusion in a companion animal comprising administering to a companion animal in need of such treatment a therapeutically effective amount of an acetylcholinesterase inhibitor.

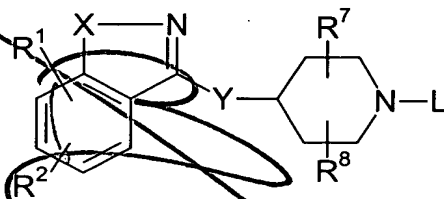
6. A method of improving the social interactions of a companion animal comprising administering to a companion animal in need of such improvement a therapeutically effective amount of an acetylcholinesterase inhibitor.

7. A method of adjusting the sleep-wake cycle of a companion animal comprising administering to a companion animal in need of such adjustment a therapeutically effective amount of an acetylcholinesterase inhibitor.

8. A method of treating inappropriate elimination in a companion animal comprising administering to a companion animal in need of such treatment a therapeutically effective amount of an acetylcholinesterase inhibitor.

9. The method of claim 1 or 3-8 wherein the companion animal is a cat or dog.

10. The method of claim 9 wherein the acetylcholinesterase inhibitor is a compound of Formula 1:

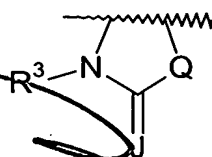


Formula 1

wherein R¹ and R² are each independently selected from the group consisting of hydrogen; (C₁-C₆) alkoxy; benzyloxy; phenoxy; hydroxy; phenyl; benzyl; halo; nitro; cyano; -COR⁵; -COOR⁵; -CONHR⁵; -NR⁵R⁶; -NR⁵COR⁶; -OCONR⁵R⁶; -NHCOOR⁵; (C₁-C₆) alkyl which may be

substituted with from 1 to 3 fluorine atoms; $\text{SO}_p\text{CH}_2\text{-phenyl}$ or $\text{SO}_p(\text{C}_1\text{-C}_6)$ alkyl, wherein p is 0, 1 or 2; pyridylmethoxy or thienylmethoxy; 2-oxazolyl; 2-thiazolyl; and benzenesulfonamide; wherein the phenyl moieties of said phenoxy, benzyloxy, phenyl, benzyl and benzenesulfonamide groups, the pyridyl and thienyl moieties of said pyridylmethoxy or thienylmethoxy groups, and the oxazolyl and thiazolyl moieties of said 2-oxazolyl and 2-thiazolyl groups may be substituted with 1 or 2 substituents independently selected from the group consisting of halo, $(\text{C}_1\text{-C}_4)$ alkyl, trifluoromethyl, $(\text{C}_1\text{-C}_4)$ alkoxy, cyano, nitro and hydroxy;

or R^1 and R^2 are attached to adjacent carbon atoms and form, together with the carbon atoms to which they are attached, a group of Formula 2:



Formula 2

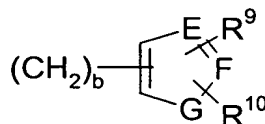
wherein R^3 is hydrogen or $(\text{C}_1\text{-C}_6)$ alkyl; J is oxygen, sulfur or NR^4 ; R^4 is hydrogen or $(\text{C}_1\text{-C}_4)$ alkyl; and Q is oxygen, sulfur, NH, CHOCH_3 , $\text{C}(\text{CH}_3)_2$, $-\text{CH}=\text{CH}-$, or $(\text{CH}_2)_l$ wherein l is an integer from 1 to 3;

X is oxygen or sulfur;

Y is $-(\text{CH}_2)_m-$, $-\text{CH}=\text{CH}(\text{CH}_2)_n-$, $-\text{NR}^4(\text{CH}_2)_m-$, or $-\text{O}(\text{CH}_2)_m-$, wherein n is an integer from 0 to 3, and m is an integer from 1 to 3;

R^5 and R^6 are each independently selected from the group consisting of hydrogen, $(\text{C}_1\text{-C}_6)$ alkyl, phenyl, and benzyl, wherein the phenyl moieties of said phenyl and benzyl groups may be substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, chloro, bromo, iodo, $(\text{C}_1\text{-C}_4)$ alkyl, trifluoromethyl, $(\text{C}_1\text{-C}_4)$ alkoxy, cyano, nitro and hydroxy; or NR^5R^6 together form a 4 or 5 membered ring wherein one atom of the ring is nitrogen and the others are carbon, oxygen or nitrogen; or NR^5COR^6 together form a 4 or 5 membered lactam ring;

L is phenyl, phenyl- $(\text{C}_1\text{-C}_6)$ alkyl, cinnamyl or pyridylmethyl, wherein the phenyl moieties of said phenyl and phenyl- $(\text{C}_1\text{-C}_6)$ alkyl may be substituted with 1 to 3 substituents independently selected from the group consisting of $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_1\text{-C}_6)$ alkoxy, $(\text{C}_1\text{-C}_4)$ alkoxycarbonyl, $(\text{C}_1\text{-C}_6)$ alkylcarbonyl, $-\text{OCONR}^5\text{R}^6$, $-\text{NHCOOR}^5$, and halo; or L is a group of Formula 3:



Formula 3

wherein b is an integer from 1 to 4; R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen, (C₁-C₄) alkyl, halo, and phenyl; E and F are independently -CH- or nitrogen; and G is oxygen, sulfur or NR⁴, with the proviso that when E and F are both nitrogen, one of R⁹ and R¹⁰ is absent; and

R⁷ and R⁸ are independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, (C₁-C₆) alkoxycarbonyl, (C₁-C₆) alkylcarbonyl, and (C₁-C₆) alkoxy, with the proviso that said (C₁-C₆) alkoxy is not attached to a carbon that is adjacent to a nitrogen; or a pharmaceutically acceptable salt or solvate thereof.

11. The method of claim 10 wherein the compound of Formula 1 is selected from the group consisting of:

5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-dihydro-7-ethyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-dihydro-3-[2-[1-(2-chloro-5-thiophenemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-dihydro-3-[2-[1-(2-methyl-4-thiazolemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(3-bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(4-bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one; and

5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one.

12. The method of claim 11 wherein the compound of Formula 1 is 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one.

13. A pharmaceutical composition for use in the treatment of an age-related behavioral disorder in a companion animal comprising a compound of Formula 1, or a

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~~pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.~~

14. The pharmaceutical composition of claim 13 wherein the compound of Formula 1 is selected from the group consisting of:

5 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-dihydro-7-ethyl-3-[2[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

10 5,7-dihydro-3-[2-[1-(2-chloro-5-thiophenemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-dihydro-3-[2-[1-(2-methyl-4-thiazolemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

3-[2-[1-(3-bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

15 3-[2-[1-(4-bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

20 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-7H-pyrrolo[5,4-g]-1,2-benzisoxazol-7-one; and

5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one.

25 15. The pharmaceutical composition of claim 14 wherein the compound of Formula 1 is 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one.

16. The pharmaceutical composition of claim 13 wherein said pharmaceutical composition is suitable for oral, rectal, parenteral, transdermal, buccal, nasal, ocular, sublingual, topical, or subcutaneous administration.

30 17. A dosage form of a compound of Formula 1 for use in the treatment of an age-related behavioral disorder in a companion animal.

18. The dosage form of claim 17 wherein said dosage form is a tablet, troche, dispersion, suspension, solution, capsule, or patch.

19. The dosage form of claim 18 wherein the compound of Formula 1 is selected from the group consisting of:

35 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;

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